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# TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

		Application Number	08/487,312
		Filing Date	June 7, 1995
		First Named Inventor	Walter L. MILLER and John D.. BAXTER
		Group Art Unit	1646
		Examiner Name	C. Saoud
Total Number of Pages in This Submission	6	Attorney Docket Number	220002016004

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<input type="checkbox"/> Fee Attached	<input type="checkbox"/> Drawing(s)	<input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences
<input type="checkbox"/> Amendment/Reply	<input type="checkbox"/> Licensing-related Papers	<input type="checkbox"/> Appeal Communication to Group (Appeal Notice, Brief, Reply Brief)
<input type="checkbox"/> After Final	<input checked="" type="checkbox"/> Petition to Reopen Prosecution under 37 C.F.R. § 1.198	<input type="checkbox"/> Proprietary Information
<input type="checkbox"/> Affidavits/declaration(s)	<input type="checkbox"/> Petition to Convert to a Provisional Application	<input type="checkbox"/> Status Letter
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Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT	
Firm or Individual Name	MORRISON & FOERSTER LLP Kate H. Murashige - 29,959
Signature	<u>Kate H. Murashige</u>
Date	May 16, 2003

BOARD OF PATENT APPEALS AND INTERFERENCES

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## CERTIFICATE OF HAND DELIVERY

I hereby certify that this correspondence is being hand filed with the United Patent and Trademark Office in Washington D.C. on May 16, 2003.

Annette Masiello

PATENT  
Docket No. 220002016004

**CERTIFICATE OF HAND DELIVERY**

I hereby certify that this correspondence is being hand filed with the United Patent and Trademark Office in Washington D.C. on May 16, 2003.

Annette Masello

Annette Masiello

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Walter L. MILLER, *et al.*

Serial No.: 08/487,312

Filing Date: 7 June 1995

For: BOVINE GROWTH HORMONE

Examiner: C. Saoud

Group Art Unit: 1646

**PETITION TO REOPEN PROSECUTION UNDER 37 C.F.R. § 1.198**

Mail Stop Petitions  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

Applicants request the written authority of the Commissioner to reopen prosecution in the above-referenced application. A decision of the Board of Appeals and Interferences affirming the sole outstanding rejection, made under 35 U.S.C. §§ 102/103 was mailed 26 March 2003.

The present application was filed as a divisional of a pending application on 7 June 1995; the earliest priority date is 26 August 1980. Considerable evidence of commercial success of the claimed subject matter has accumulated between the time prosecution was closed in this case and the present, and applicants believe they should be afforded an opportunity to present this evidence. As the earliest priority date in this line of cases is 26 August 1980, applicants are

sd-146762

unable to present this evidence in the context of a continuing application. Accordingly, for the reasons described more fully below, applicants request that prosecution be reopened in the present case to permit them to submit the evidence enclosed with this petition.

Background Information

The claims in the present application are directed to bovine growth hormone that is recombinantly produced by a method that comprises culturing cells that contain a recombinant DNA molecule encoding a specific amino acid sequence or an allelic variant thereof. A copy of the claims currently pending is attached as Exhibit A. The application itself is a divisional of Serial No. 07/480,745 filed 15 February 1990 which was the subject of an Interference decided in favor of the present applicants on October 16, 2002. The '745 application is the great-granddaughter through a series of continuations of an application 06/181,348 filed 26 August 1980. The present application was filed prior to 8 June 1995 and thus, if issued, would have a term of 17 years from issue. However, applicants are unable to file a continuing application since the earliest priority date that must be claimed is 26 August 1980 which would result in an expiration date of 26 August 2000.

In the present application, a final rejection was mailed on 16 October 1996 and a Notice of Appeal was filed 16 January 1997. Since this time, considerable evidence has accumulated showing dramatic commercial success of the claimed subject matter. Any commercial success, as has been argued extensively in the present record, is directly attributable to the recombinant nature of the bovine growth hormone claimed. As the bulk of the commercial success experienced by this product has been demonstrated since the close of prosecution, applicants believe that prosecution should be reopened to permit applicants to make this documentation of

record. Because this evidence was not of record herein, the Board of Patent Appeals and Interferences correctly refused to consider this accumulated evidence at Oral Hearing.

Evidence of Commercial Success

The protein claimed in claims 19, 20 and 22 (exhibit A) is marketed by Monsanto under the trademark Posilac®. Active marketing efforts did not begin until 1994 when the product was finally approved. Substantial evidence of commercial success was only beginning to develop at that time. The Monsanto website of February 3, 1997, attached as Exhibit B, describes the success achieved since the initial entry into the market of this product in February 1994. As indicated in this exhibit, Monsanto states that 15-20 new dairy producers joined the Posilac™ program each business day and more than 15% of all dairy producers in the U.S. purchased this product. An update, published July 1, 1997, by Monsanto (Exhibit C), states that by then 25% of the cows in the U.S. are in herds that are supplemented with Posilac™. A status update published May 11, 1999 (Exhibit D), states that 1996 sales were up 45% over 1995; 1997 sales were up 30% over 1996; and 1998 sales were up 30% over 1007. This publication notes that the Institute of Food Science and Technology in Great Britain concluded that there were no harmful effects of the recombinant material - this is the face of prevalent Mad Cow Disease in Great Britain.

A January 1999 article in the *St. Louis Post Dispatch* (Exhibit E) indicated that in 1998, the sales of Posilac™ were estimated at \$200,000,000, a lower figure than reported in (Exhibit F) from the *Chicago Tribune* webpage which estimates these sales at \$600,000,000.

An article published in 2000 (Exhibit G) states that in a time span of six years, approximately 35-40% of U.S. dairy herds have adopted the use of Posilac™. This article also provides a comparison of the fate of recombinant bovine growth hormone in the U.S. and

Europe. The final page of this article compares the factors that led to the acceptance of recombinant bovine growth hormone in the U.S., but rejection in Europe. The first factor listed with regard to the European rejection is the negative spillover from what was perceived as Europe's poor public relations and regulatory handling of Mad Cow Disease. Clearly, the nexus between Mad Cow Disease and the damage posed by animal as opposed to recombinant products is a factor in weighing commercial acceptance.

Thus, it is not unreasonable to state that the success of recombinant bovine growth hormone in the United States is dependent on the ability of Monsanto to guarantee that the infectious agent from Mad Cow Disease is not present in the recombinant product. It is this *inherent* property of recombinant bovine growth hormone that is responsible for its commercial success. This claim limitation can thus be shown to provide the required basis for commercial success. Thus, evidence of this commercial success is highly relevant in evaluating the patentability of the claimed subject matter. The evidence included with this petition with regard to the great commercial success of recombinant bovine growth hormone could not have been earlier presented effectively.

#### The Precedential Effect of Recombinant Factor VIII

On April 8, 1997, U.S. patent 5,618,789 was issued. This was subsequent to the effective close of prosecution in the above case. Claim 1 of the issued patent is directed to "A composition comprising a recombinant functional human factor VIII free of viral contaminants that affect humans in a pharmaceutically acceptable carrier."

The basis for assertion that the factor VIII was free of viral contaminants was simply that it was recombinantly produced.

While factor VIII had previously been purified from human blood, this patent issued with claims to the recombinant form. Applicants believe that this patent establishes a precedent relevant to the present claims. As these claims issued subsequent to the close of prosecution, applicants request that prosecution be reopened so that this, too, may be presented.

For the reasons stated above, applicants respectfully request that prosecution be reopened in this case.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. **220002016004**.

Respectfully submitted,

Dated: May 15, 2003

By: Kate H. Murashige  
Kate H. Murashige  
Registration No. 29,959

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**EXHIBIT A. - THE CURRENTLY PENDING CLAIMS**

19. Bovine growth hormone produced by a method which comprises culturing cells which contain a recombinant DNA molecule which DNA molecule comprises a nucleotide sequence encoding bovine growth hormone comprising the amino acid sequence at positions 2-191 of Figure 1 or an allelic variant thereof, said encoding nucleotide sequence contained in an expression system effective in producing said encoded bovine growth hormone in a recombinant host cell,

    said culturing under conditions wherein the encoding nucleotide sequence is expressed to produce said bovine growth hormone; and

    recovering the bovine growth hormone from the culture.

20. The bovine growth hormone of claim 19 which comprises the amino acid sequence at positions 2-191 of Figure 1.

22. The bovine growth hormone of claim 19 which is in purified and isolated form.

## Status Update: POSILAC® Bovine Somatotropin

**February 3, 1997**

### **General background:**

- POSILAC bovine somatotropin continues to gain wide acceptance and use as a management tool to enhance dairy cow productivity. Since POSILAC was introduced in February 1994, at least 17,000 dairy producers, or more than 15 percent of all dairy producers in the U.S., have purchased the product.
- In its first two years, POSILAC became the largest selling dairy animal health product in the United States. Sales of POSILAC increased significantly in 1995 over 1994 -- in the range of 15 to 20 percent. For 1996, sales volumes were up 45 percent from 1995.
- As POSILAC enters its fourth year of commercial sales, Monsanto confirms the steady growth of the product in terms of sales, total number of cows receiving the product and percentage of cows within herds receiving the product. Reflecting the acceptance and growth of this product is the fact that 15 to 20 new dairy producers are joining the POSILAC program each business day.
- To date, dairy producers across the United States have used more than 50 million doses of POSILAC.
- Most dairy operators using the product are supplementing 40 to 70 percent of their cows at any one time. Customer usage rates vary depending on individual herd management practices and stage of adoption.
- Dairy farmers continue to report excellent results with POSILAC -- over 99 percent of producers using POSILAC report increases in milk production. POSILAC users report productivity increases of 5 to 15 pounds per day per cow.
- Satisfied customers across the United States, many with three years experience, attest to the product's safety. Further, the FDA confirms that no unusual or unexpected concerns about cow or human safety have been raised since POSILAC's introduction.
- POSILAC has proved itself to be an effective management tool that helps dairy producers, both large and small, improve their operations, lower their cost for producing high quality milk and achieve higher profitability.
- Monsanto estimates that U.S. dairy producers using POSILAC have realized a combined total of over \$300 million in additional profit since the product was launched in February 1994.
- Monsanto's data show that the size of herds supplemented with POSILAC closely resemble the distribution of herd size found in the U.S. Nearly 55 percent of the farmers using POSILAC manage herds of 100 cows or fewer. This underscores the fact that both large and small dairy operations are benefiting from the product.
- The U.S. Food and Drug Administration, World Health Organization, American Medical Association, American Dietetic Association and regulatory agencies in 30 countries agree that the milk from cows supplemented with POSILAC is the same safe, wholesome product as it always has been.

### **Three Years of Actual Marketplace Experience:**

- The use of POSILAC as a dairy production tool has not affected the health of dairy cows, nor has it affected the safety of the U.S. milk supply. POSILAC is safe for dairy cows and for the consumers of dairy products.
- All clinical signs observed in the customer experience data base for POSILAC occur normally in lactating dairy cows. Data from the first two years in the market show that the rate of adverse experiences, including mastitis, are well below or within the range of reported incidence for those conditions in the U.S. dairy herd.
- The use of POSILAC has had no effect on milk safety.
  - Milk discard data collected over four years from states representing over 50 percent of the U.S. milk supply show no increase in milk discarded because of violative residues as a result of use of POSILAC.
  - There is no relationship between the extent of the use of POSILAC within a given state and the percentage of milk discarded because of violative antibiotic residue.
- Industry surveys confirm there have been no increase in reported cases of mastitis or in the sale of antibiotic agents used to treat mastitis in dairy cows, since POSILAC entered the market.
- Recent improvements by the dairy industry in monitoring milk safety provide even more reason for confidence in the safety of the U.S. milk supply than in the past. Post-pasteurization testing by FDA confirms the basis for such confidence at the consumer level. For example, during the fourth quarter of 1995 the National Drug Residue Milk Monitoring Program randomly tested 21,510 samples of milk after it had left processing facilities. Not a single case of violative residues was found.

### **Monsanto's Continuing Customer Outreach:**

- Monsanto's customer outreach has been unprecedented and the most rigorous for any new animal health or productivity-enhancing product in recent history. Because Monsanto sells directly to producers, the company has regular contact with every single customer. It enables Monsanto to assess producer experience with POSILAC in unique detail and without undue delays.
- As part of its outreach, Monsanto proactively contacts customers on an ongoing basis, in addition to staffing an 800-number for incoming calls. Over the past two plus years, the program has resulted in over 247,000 telephone calls with customers. This means that each customer averaged 14 phone conversations with Monsanto's sales staff.
- As an added means of supporting dairy producers, Monsanto works within the network of the feed and animal health industries. This technical support system notifies the company if they encounter any health problems in cows receiving the product. In addition, they work with producers to help improve nutritional and management practices.

- Monsanto is committed to working with any producer who experiences dairy management problems, or who has other concerns, to ensure the experience with POSILAC is successful.

*POSILAC® is a registered trademark of Monsanto Company.*

# Posilac® Bovine Somatotropin Status Update

July 1, 1997

## General Background

### The Post Approval Monitoring Program (PAMP) For POSILAC Monsanto's Continuing Customer Outreach

## GENERAL BACKGROUND

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- POSILAC bovine somatotropin continues to gain wide acceptance and use as a management tool to enhance dairy cow productivity. Of the more than 8.9 million cows in the United States, approximately 25 percent of the cows are in herds that are supplemented with POSILAC.
- During its first three years, POSILAC became the largest selling dairy animal health product in the United States. Sales of POSILAC continue on a strong growth curve with a 40 percent increase in volume in the first five months of 1997 compared to the same time period in 1996. For 1996, sales volumes were up 45 percent from 1995.
- As POSILAC enters its fourth year of commercial sales, Monsanto confirms the steady growth of the product in terms of sales, total number of cows receiving the product and percentage of cows within herds receiving the product. Reflecting the acceptance and growth of this product is the fact that more than 400 dairy producers are joining the POSILAC program each month.
- In early 1997, POSILAC reached a milestone with more than 50 million doses delivered.
- The average dairy operator using POSILAC is supplementing more than 50 percent of the herd at any one time. Customer usage rates vary depending on individual herd management practices and stage of adoption.
- Dairy farmers continue to report excellent results with POSILAC -- over 99 percent of producers using POSILAC reported increases in milk production. POSILAC users report productivity increases of 5 to 15 pounds per day per cow.
- Satisfied customers across the United States, many with more than three years experience, attest to the product's safety. Further, the FDA confirms that no unusual or unexpected concerns about cow or human safety have been raised since POSILAC's introduction.
- POSILAC continues to prove itself to be an effective management tool that helps dairy producers, both large and small, improve their operations, lower their cost for producing high quality milk and achieve higher profitability.
- Monsanto's data show that the size of herds supplemented with POSILAC closely resemble the distribution of herd size found in the United States. Nearly 55 percent of the farmers using POSILAC manage herds of 100 cows or fewer. This underscores the fact that both large and small dairy operations are benefiting from the product.
- The U.S. Food and Drug Administration, World Health Organization, American Medical Association, American Dietetic Association and regulatory agencies in 30 countries agree that the milk from cows supplemented with POSILAC is the same safe, wholesome product as it always has been.

## THE POST APPROVAL MONITORING PROGRAM (PAMP) FOR POSILAC

top

**POSILAC<sup>®</sup> 1 STEP****Status Update: POSILAC<sup>®</sup> bovine somatotropin****May 11, 1999****General Background:**

- POSILAC bovine somatotropin continues to gain wide acceptance and use as a management tool to enhance dairy cow productivity. Of the nearly 9 million dairy cows in the United States, approximately 30 percent of the cows are in herds that are supplemented with POSILAC.
- Approximately 13,000 dairy producers are currently taking advantage of the benefits offered by POSILAC. The product is sold in all 50 states. Dairy producers using POSILAC have herds sizes ranging from 5 cows to over 10,000 cows.
- As POSILAC enters its sixth year of commercial sales, Monsanto confirms the steady growth of the product in terms of sales, total number of cows receiving the product and percentage of cows within herds receiving the product. Reflecting the continual growth and acceptance of this product is the fact that approximately 300 dairy producers per month have been joining the POSILAC program over the last three years.
- Since its introduction in 1994, POSILAC has become the largest selling dairy animal health product in the United States. Sales of POSILAC continue on a strong growth curve.

Sales growth in recent years is summarized below:

1998 sales are up nearly 30 percent over 1997;  
1997 sales were up 30 percent over 1996; and  
1996 sales were up 45 percent over 1995.

- In 1998, POSILAC achieved a significant milestone with more than 100 million doses delivered.
- To help meet growing world demand for POSILAC, construction is nearing completion on a new multi-million dollar manufacturing facility in Georgia.
- The average dairy operator using POSILAC is supplementing more than 50 percent of the herd at any one time. Customer usage rates vary depending on individual herd management practices and stage of adoption.
- Dairy farmers continue to report excellent results with POSILAC - over 99 percent of producers using POSILAC reported increases in milk production. POSILAC users report productivity increases of 5 to 15 pounds per day per cow.

- Satisfied customers across the United States, many with over five years experience, attest to the product's safety. Further, the FDA confirms that no unusual or unexpected concerns about cow or human safety have been raised since POSILAC's introduction.
- POSILAC continues to prove itself to be an effective management tool that helps dairy producers, both large and small, improve their operations, lower their cost for producing high quality milk and achieve higher profitability.
- Monsanto's data show that the size of herds supplemented with POSILAC closely resemble the distribution of herd size found in the United States. Nearly 55 percent of the farmers using POSILAC manage herds of 100 cows or fewer. This underscores the fact that both large and small dairy operations are benefiting from the product.

### **Third Party Confirmation of POSILAC Safety:**

- The U.S. Food and Drug Administration, World Health Organization, American Medical Association, American Dietetic Association and regulatory agencies in 30 countries agree that the milk from cows supplemented with POSILAC is the same safe, wholesome product as it always has been.
- On March 5, 1998, the Food and Agriculture Organization (FAO) of the United Nations released a committee report reconfirming that treating cows with POSILAC to increase milk production is safe. After examining new evidence, the joint FAO-World Health Organization expert committee concluded that "there are no food safety or health concerns related to BST residues in products such as meat and milk from treated animals." For more information see the FAO press release or the committee's summary and conclusions report.
- The Institute of Food Science and Technology (IFST), located in Great Britain, through its Public Affairs and Technical and Legislative Committees, has issued an update to its Position Statement on BST dated 11 June 1998, the summary of which is that "... the use of bovine somatotropin (BST) to improve milk yield in cows indicates that it carries no harmful effects to humans, to the treated animals or to the environment; the resulting milk and meat is not significantly different from milk and meat from untreated cows, in composition or quality; and in consequence there is no scientific or ethical basis for requiring distinctive labelling of milk or meat from BST treated cows."

### **The Post Approval Monitoring Program (PAMP) for POSILAC:**

- In November 1996, the Monsanto Dairy Company received unanimous support from the Veterinary Medicine Advisory Committee (VMAC) of the Food and Drug Administration regarding the results of the most extensive post-approval monitoring program (PAMP) ever conducted for an animal health product.
- The program was designed to collect additional information about supplementation with POSILAC in on-farm settings, evaluate the adequacy of established product use instructions and determine whether the product affects the quality or safety of milk. PAMP was voluntarily conducted and developed by the Monsanto Dairy Company, with final review from the FDA.
- The PAMP for POSILAC was initiated in 1993, and consisted of three components: an Adverse Drug Experience (ADE) reporting system, analysis of state antibiotic drug residue data, and a health evaluation of 28 commercial dairy herds.
- The collecting of ADEs for POSILAC was highly proactive and was unprecedented for an animal product. Within this part of PAMP, farmers' experiences with the product were actively sought and recorded. Each customer was contacted an average of 14 times, which ensured a uniquely comprehensive history of the use of POSILAC and ADEs.
- The ADE evaluation found that conditions in herds supplemented with POSILAC were either within or well below the range reported of similar instances in non-supplemented dairy herds. All of the reported concerns commonly occur in dairy cows.
- In 1994, the year POSILAC entered the market, there was no difference in the percentage of milk discarded due to violative residues, as compared to 1992 and 1993.
- During a two-year period, POSILAC was studied in 28 commercial dairy herds in four regions across the country. The study, representing 1,213 cows, focused on the general herd health in commercial operations ranging from 40 to more than 1,500 head per herd.
- The results of PAMP confirmed the safety of POSILAC for cows and the safety of the milk supply from cows supplemented with POSILAC.

### **Monsanto's Continuing Customer Outreach:**

- Monsanto's customer outreach has been unprecedented and the most rigorous for any new animal health or productivity-enhancing product in recent history. Because Monsanto sells directly to producers, the company has regular contact with every single customer. It enables Monsanto to assess producer experience with POSILAC in unique detail and without undue delays.

- As an added means of supporting dairy producers, Monsanto works within the network of the feed and animal health industries. This technical support system notifies the company if they encounter any health problems in cows receiving the product. In addition, they work with producers to help improve nutritional and management practices.
- Monsanto is committed to working with any producer who experiences dairy management problems, or who has other concerns, to ensure the experience with POSILAC is successful.

*POSILAC® is a registered trademark of Monsanto Company.*

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**POSILAC® Current Information Index**    **POSILAC® Home Page**

Date: 25 Jan 1999 22:43:39 -0600  
From: Judy\_Kew@greenbuilder.com (Judy Kew)  
Subject: Monsanto gets new federal OK on GM milk hormone

Forwarded by  
NATURAL LAW PARTY WESSEX  
nlpwessex@bigfoot.com  
www.btinternet.com/~nlpwessex

Monsanto gets new federal OK on milk hormone

ST. LOUIS -- Reaffirming that a Monsanto Co. (MTC) drug is safe, the nation's top health officer has rejected appeals from critics to pull the genetically engineered product from the market. Donna E. Shalala, secretary of health and human services, said the critics of BST -- the drug that increases cows' milk production -- have raised "no new scientific concerns" about the drug's safety. That means the Food and Drug Administration, which reports to her, "does not intend to remove the product from the market," Shalala said in a letter sent Thursday to Vermont Sens. Patrick J. Leahy and James M. Jeffords. After a slow start, the drug, sold under the brand name Posilac, has recorded higher sales each year. Last year, it produced an estimated \$200 million in revenue. Canada's top health agency, HealthCanada, rejected BST last week. (St. Louis Post-Dispatch)

Compiled by CBS MarketWatch  
Last Update: 2:00 PM ET Jan 23, 1999

EXHIBIT E

Monsanto Growth Hormone Used in About 30% of U.S. Dairy Cows

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>Chicago, Jan. 2 (Bloomberg) -- About 30 percent of the nation's dairy cows  
are

>supplemented with bovine somatotropin, a synthetic growth hormone sold by  
>Monsanto Co. under the name Posilac, even though it was once viewed as a  
>threat to small producers because it would increase milk production and lower  
>prices, the Chicago Tribune reported. The product, otherwise known as BST,  
was

>approved for use five years ago and can increase milk output per cow about 10  
>percent per day, according to St. Louis-based Monsanto. In 1998, total sales  
>of Posilac passed 100 million doses and Monsanto's revenue on the product  
>reached \$600 million, the paper said.

>

>Thursday, Monsanto won approval from the Food and Drug Administration to sell  
the first drug in a new class of painkillers for arthritis.

>

>(CT 1/2 2-1 [www.chicagotribune.com](http://www.chicagotribune.com))

***EXHIBIT G*****G** Search

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## Regulation Of rbST In The US

**Robert Collier**

The University of Arizona

*In the United States (US) and European Union (EU) the regulatory and commercialization process for recombinant bovine somatotropin (rbST) had widely differing outcomes. Although the regulatory process in both locations was completed in 1993 the commercialization of rbST in the US has been highly successful while completely failing in the EU. This paper examines these events from the US perspective and concludes that reasons for the difference in commercial success lie in the cultural, regulatory, and political background differences between the two world locations.*

**Key words:** somatotropin; dairy cattle; regulatory process; public acceptance.

This paper provides a US perspective on the approval and regulation of recombinant bovine somatotropin (rbST). It also provides a chronology of the key events that have taken place in the US, as well as in the EU with respect to rbST. This paper is organized as follows: the present status of rbST in the US and Europe is reviewed first. A brief historical overview of how the US and the EU reached their current positions on rbST is given next. Finally, the factors that led to the differing outcomes in the EU and the US are delineated, along with lessons that have been learned from the case of rbST. Parallels are drawn with current developments in genetically modified (GM) foods.

### The Current Status Of rbST

In the US, Posilac® is the brand name of Monsanto's rbST, a two-week formulation administered by subcutaneous injection in lactating dairy cows. It is the largest selling pharmaceutical product in the history of the dairy industry. In a time span of 6 years, approximately 35-40 percent of US dairy herds have adopted use of Posilac®. This parallels fast adoption rates of other non-agricultural biotechnologies.

Technical approval of rbST was achieved in the EU in 1993, the same year as the US. However, in the EU there is currently a ban on rbST sales and research. This ban remains in place indefinitely, even though the human safety of rbST has been reaffirmed by both the US and EU, and milk and milk products from cows injected with rbST in the US are not prevented from entering the European Union, therefore, no trade barriers exist to milk products from US dairy cattle treated with rbST.

The differing EU and US regulatory approval outcomes have taken place in a constantly changing period for world agriculture. Worldwide, high yield, intensified agriculture is being scrutinized for its environmental, human health impacts as well as its effects on land and water resources.

as its effects on land use and rural human communities. Projected world population growth, and the increasing need for advances in agricultural productivity to provide safe and nutritious food for animals and humans while protecting the environment are continual issues. The public debate on the use of biotechnology, and the public's concerns of chemical-use in agriculture and its links to human health, have been dominant frames throughout the period of rbST approval and commercialization process. However, these and other similar factors have played out differently in EU and the US. The approval process was successful in both locations, it was the commercialization process that differed. This paper attempts to answer why this may be the case.

### The History Of rbST

The effects of bovine somatotropin (bST) in cattle were first reported by two Russian scientists, Azimov and Krouze (1937). These investigators found that an active principle extracted from the pituitary glands of cows increased milk production. Their study, published in the *American Journal of Dairy Science*, was seminal in the field. Their major conclusions from this study indicated there were no adverse effects on cow health, a consistent increase in milk yield that was influenced by the quality of management of the farm, and that milk yield returned to previous levels after completion of treatment. These findings still hold true today. The active compound in the pituitary extracts was later identified as bST (Young, 1947). During World War II, English scientists confirmed the effects of somatotropin in goats, as well as cows, and considered it a potential way to increase food production (Cotes *et al.*, 1949). However, these scientists were unable to supply enough somatotropin from slaughterhouse-derived pituitaries to make it a practical reality.

In the 1960s, Monsanto initiated a research program in bST (Machlin, 1972). Monsanto, a chemical company at that time, saw a business opportunity if a chemically synthesized fragment of the bST molecule that was active could be found. This active fragment would then be used to duplicate all the effects of bovine somatotropin. Following extensive scientific studies it was discovered that all 190 amino acids would be needed in order to simulate the desired effects of bST. At the time, a protein that large could not be chemically synthesized. So the program was terminated and all the scientists were assigned to other projects or laid off. Yet the program had left its mark on Monsanto, as it signaled a large business opportunity, if another way to produce bST could be found. Hence, the stage was set for recombinant bST or rbST.

1973 was a pivotal year for chemical companies, such as Monsanto, because this was the year of the world oil crisis. Operating profit at Monsanto dropped 88 percent as a result of oil price increases. Monsanto realized its profits were directly tied to oil and that it would need to eliminate this dependency in the future. Biotechnology was seen as an opportunity to get away from this dependency. So Monsanto invested in a number of biotechnology companies, one of which was a startup company called Genetech. Between 1973 and 1981, through a series of consultations, Genetech agreed to produce rbST for Monsanto. Genetech produced Monsanto's first bovine somatotropin, being the first animal molecule that it cloned, (Leonard-Barton & Pisano, 1993).

By 1982, efficacy trials of rbST had begun in the US. These trials set out to determine if a full lactation increase was possible, because previous studies had only used small amounts of material. No one had yet proven that a cow could be treated through the entire lactation period and still remain healthy. At Cornell University, Professor Dale Bauman (Bauman *et al.*, 1985) conducted the initial studies and demonstrated that cows remained healthy while maintaining an increase in milk production.

By 1983, Monsanto had committed to a worldwide effort to get rbST approved, and

had started European trials, as well as continuing the US trials. Opposition to rbST in Europe started earlier than in the US and was based on concerns about food safety and impact on small farms. The first hint that there might be a backlash in the US came following an economic study conducted by Kalter *et al.* (1985) at Cornell University. Kalter *et al.* (1985) utilized results from the first full lactation study conducted at Cornell University (Bauman *et al.*, 1985) which had reported that at the highest application dose milk production could increase by as much as 40%. Kalter *et al.* (1985) suggested that if rbST was rapidly adopted in the dairy industry, with a resultant 40% increase in milk production, about 30% of dairy farmers would go out of business within 5 years of approval. This study immediately got the attention of the dairy industry, particularly its implications for the dairy industry worldwide. Of course, the scenario of a 40% increase in milk production was just one potential outcome. In fact, the average increase is approximately 15% which is similar to the effect of switching from 2 times to 3 times daily milking, a common practice in the dairy industry (Bauman, 1992). Concerns about impacts on small farms and milk prices had the effect of uniting some farming groups with consumer activists opposed to the new technology.

Between 1985-1986 there was much anti-rbST activity, mostly on the part of consumer advocates, such as Jeremy Rifkin, who were opposed to biotechnology. The Green Movement in Europe was also active in what at that time Monsanto considered to be low-key opposition to the technology. Ironically, the first rbST plant was built in Europe because it was considered highly likely that European approval would occur first. In fact, a survey of consumers in the United Kingdom (UK) in 1985 indicated that more than 70% believed the initials BST stood for British Summer Time.

In 1987, the first submissions were made for approval in France, the UK, and in the United States. At that time, submissions were made to member countries intended as markets for the product. France and the UK were two European markets that were initially selected.

The first large investigation of the rbST approval process in the US started in 1989 when Senator Leahy of Vermont requested a General Accounting Office (GAO) investigation (GAO, 1994). The debate at this point was not only public but was also becoming political. By 1990, the EU had established a moratorium on rbST approval until the end of the year. This moratorium was imposed just in case approvals occurred, and in order to ensure that EU countries would not market the product. In the United States, the National Institutes of Health (NIH) held a public hearing and reviewed the human safety aspect of rbST, reaffirming its safety (NIH, 1991).

Public hearings similar to those conducted in the US were never held in Europe. In the US, investigations were public—the GAO (GAO, 1994) and the Inspector General's (IG) Office (Kusserow, 1992) were involved in the review process and their findings were released as public documents. These debates exposed the issues and allowed the public to get involved. They were all open; anyone could attend hearings and seek permission to speak. A large number of groups did. In Europe, however, there was almost no public discussion.

The Office of Technology Assessment (OTA) in the US issued a report in 1992 (OTA, 1992), the same year as the EU extended its moratorium on rbST. This report, along with a report from the US Inspector General's Office, found that the processes by which safety data was collected, or how the Food and Drug Administration (FDA) provided oversight of the technology were appropriate. Monsanto received its final favorable opinion from the Committee of New Medical Products (CVMP) in 1993. At about the same time, the FDA held a public hearing on concerns expressed about mastitis being caused by the use of rbST in cattle. The Veterinary Medical Advisory Committee (VMAC) chaired a public hearing on the mastitis issue alone, which was also published (Collier, 1993). In 1993, there was also a ninety-day moratorium placed on rbST sales that was enacted by congress and allowed the FDA to develop a

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Post-Approval Monitoring Program (PAMP) to evaluate impact of rbST use in the dairy industry on cattle health and milk quality. These results were presented in two public hearings after 6 and 12 months of commercial sales.

Late in 1993, the FDA approval process was completed in the United States. In the EU, the moratorium placed on rbST was extended with almost no public debate. The only debate carried out in Europe was in the press. Meanwhile, in the United States sales began in 1994 with the FDA issuing guidelines for voluntary labeling. At the same time that sales began, the PAMP was initiated to reassure consumers that Posilac® labels were accurate that there were no changes in the safety of the milk supply. The occurrence of antibiotics in milk was monitored for 50 percent of the US milk supply.

Monsanto markets Posilac® directly to producers so that every time a producer ordered the product, they could be queried on any concerns they may have regarding product safety. Farmers indicating any concerns about treated cows automatically became adverse experiences and were reported to the FDA. This was probably the most extensive PAMP ever carried out on an animal drug, and the results of this program were publicly reported. There were two post-approval periods—6 months and one year post-approval. In addition, the FDA issued reports every 6 months on adverse experience indications and any other concerns that might have arisen. Hence, there was in-depth oversight and monitoring during the early introduction of rbST. In 1994, the EU extended the moratorium for a further 5 years. In 1999, the FDA reaffirmed the safety of rbST for humans in direct response to a letter from some members of congress. In 1999, Canada rejected the somatotropin license that Monsanto had submitted. This rejection was based on cow health concerns. In 1999, the EU extended the moratorium to an outright ban.

### **How US Consumer Concerns Were Addressed**

The fundamental concerns of US consumers were not substantially different from those in other regions of the world. United States consumers were concerned about the impact of rbST on small farms, human food safety, and animal welfare. Much work was done in response to these concerns. There have been several independent studies carried out which examine the impact of rbST on small farms, specifically in regard to the impact on herd size, the longevity of cows in the herd, as well as, the kinds of problems experienced in implementing the technology (Bauman et al., 1999; Judge et al., 1997; Ruegg et al., 1998; Van Amburgh et al., 1997; Tauer & Knoblauch, 1997). Probably the most notable of these studies was one conducted on herds located in the Northeastern United States (Bauman et al., 1999). These were small dairies in the Northeast—herds were not greater than 250 dairy cows in most cases. This study compared the lactation records of farms that adopted rbST five years post-approval and treated at least fifty-percent of the herd to those that never adopted use of rbST during the same time period. The study demonstrated that in herds adopting use of rbST, the herd size increased; adopting farms were also able to invest more; there was no change in longevity of cows in the herd; there was no difference in the reproductive performance of the herd, and there was no difference in mastitis incidence. In another study, (Tauer & Knoblauch, 1997) increased profits from the use of Posilac® were reinvested in the farm but no size bias was shown.

The human food safety impact of rbST was also studied closely. Each evaluation has been carried out in a public forum. The FDA has repeatedly provided opportunities for the public to openly participate in evaluating the human safety component of rbST. Information provided by studies on human health demonstrated safety (Juskevich & Guyer, 1990; Hammond et al., 1990). Third parties were very important to the debate. For instance, the American Cancer Society negated concerns that rbST could potentially be carcinogenic. Then the animal welfare component was essentially evaluated in the PAMP, and again there were two public hearings that allowed open

participation. These meetings were heavily covered in the farm press.

### The Safety Of rbST

When a cow is treated with rbST the concentration of bST in milk does not change. This is one of the reasons why a cow cannot be detected that has been treated with rbST. The concentration of rbST in milk is extremely low—about one part per billion. When milk is pasteurized—and there is only one dairy in the US that does not pasteurize milk—the rbST is destroyed. This is independent of the fact of that the concentration of bST in milk does not change when you treat a dairy cow with rbST. When milk is consumed the somatotropin is broken down like every other protein. There are hundreds of proteins in milk, of which somatotropin is an extremely small component. Casein is the primary milk protein that makes up 85% of the protein in milk and this is considered a "foreign protein." The term "foreign protein" has been used in the public arena to increase the perceived risk of the technology on the part of the public. Foreign proteins, however, are a normal part of foods that humans consume.

Concerns voiced about rbST include the fact that its concentration would increase in milk, that it can escape destruction of pasteurization and digestion, and that it will have a biological effect—usually something like cancer. Based on existing knowledge, as explained above, the probability of such a series of events occurring is not measurable. To this even it should also be added that studies have shown (Juskevich & Guyer, 1990) that if a person is injected with somatotropin there are no detectable effects. It does not bind to the human growth hormone receptor (Hammond et al., 1990).

Another safety concern has been made that cows treated with rbST will experience more mastitis, causing dairy farmers to use more antibiotics, which, in turn contaminate milk and cause allergic reactions in people. It is a proven fact that with an increase in milk production there is an increase in mastitis. This is part of the body of evidence that has accumulated under the mastitis review process (White et al., 1994). The use of antibiotics is an individual management decision on the part of the dairy farmer. Some farmers use antibiotics intensively while others do not—usage can vary quite dramatically. But even if a dairy farmer did use antibiotics more intensively a series of events would have to occur in order for those antibiotics to end up in the milk supply. At each point in the supply chain—from the dairy farmer to the consumer—the milk is sampled and tested. Hence, the truck driver who collects the bulk tank of milk takes a sample from every milk tank that they collect at the farm. Every truck that delivers to the processing plant is then sampled. When the milk goes into the silo it is sampled every day. If any sample is found to contain antibiotics it is disregarded. It is therefore extremely unlikely that a contaminated sample would be delivered to retail stores for human consumption. It is very difficult to get an antibiotic concentration in milk high enough to cause a serious problem within the human population.

### Labeling Of rbST

The United States has made significant progress on labeling. Labeling has to be truthful and it has to be informative. The basis for mandatory labeling is a change in the characteristics of the food being sold, for example, if an ingredient is added, or if the concentration of some ingredient is changed. Labeling a food product based on production practices may be done on a voluntary basis appealing to interested consumers while still making valid claims. In the case of rbST, the biotechnology industry supported voluntary labeling other voluntary labels include organic milk and cheese, which allows for the use of recombinant rennet (chymase) produced through biotechnology.

## Lessons Learned From rbST

There are several lessons that can be learned from the acceptance of rbST in the United States and its rejection in the European Union.

### *Factors in US Acceptance of rbST*

- One of the key factors that facilitated the commercialization and acceptance of rbST in the US was that the political process did not interfere with the ability of Monsanto to continue conducting its research and studies. If a firm or university can not provide data for regulators to evaluate, there is no way to satisfy questions about safety. Because Europe did not allow Monsanto, or any other university or firm for that matter, to conduct safety studies, it greatly reduced the chance of rbST being approved.
- Another important factor was the elimination of dairy subsidies in 1985. The case could no longer be made that Monsanto was being subsidized through increases in milk production paid by taxpayers. The price support in place was so low that it was never triggered in the post approval period.
- Similarly, the congressional hearings were highly publicized in the US, which allowed not only attendance by members of the national press but also the farm press. The hearings were well covered and highly commented on so that the public as a whole was kept aware of recent developments.
- Third parties also participated in the public debate. These parties were considered to be independent and reliable sources of information by the public. Independent sources included the American Pediatric Society, the American Cancer Society, the Dietetic Association, and so on. All of these groups were able to provide direct, reliable sources of information to consumers.
- Finally, the PAMP that was carried out in the US was very successful. Similarly, the voluntary labeling program allowed milk to be labeled from cows not treated with bovine somatotropin, as long as there were no health claims made that the milk was any different. Voluntary labeling allowed people seeking non-rbST milk to find it.

### *Factors in European Rejection of rbST*

The EU situation, however, was different from that in the US.

- Bovine spongiform encephalopathy (BSE) or "mad cow" disease set the stage for a low level of confidence in the EU regulatory process. The formation of the European Union changed how the whole food regulatory process was structured. This led to an unfavorable climate towards acceptance.
- A parallel ban on steroid (non-peptide) growth hormones created yet another negative influence on public attitudes.
- The Green Movement came out strongly against biotechnology. This stance ultimately contributed to the negative climate of public opinion in Europe.
- The European press became very polarized about biotechnology. It did not report two sides to the story, and before very long the public was polarized as well.
- The policy environment was equally unsuitable. The EU's common agricultural policy (or CAP), directly subsidizes milk output. An increase in milk production from the use of rbST would therefore lead to a perceived increased cost of the subsidies. This effect was unpalatable both from the government's and from the public's perspective. In all, there was little support for somatotropin in Europe.

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